

Porous organic polymer mouldings

The invention relates to porous organic polymer mouldings which, owing to their properties, are particularly suitable as chromatographic separation materials, and to the production thereof by means of an imprinting process.

Polymeric mouldings are widely used as chromatographic separation materials. Known uses are of organic polymeric membranes for the separation of macromolecular substances (EP 0 320 023) and of porous silica gel mouldings instead of the conventional particulate sorbents for chromatographic separations (WO 95/03256). Silica gel mouldings can be produced with a defined narrow pore distribution. Through the combination of mesopores and macropores, good separation efficiencies can be achieved, even at a high flow rate. In this way, mouldings offer more advantageous properties than particulate support materials.

However, a disadvantage of silica gel mouldings is their inadequate stability in aqueous eluents, in particular at pH values > 7 . For this reason, they cannot be employed for all chromatographic separation methods, such as, for example, ion exchange chromatography. Furthermore, there are restrictions in the purification and antifouling treatment of silica gel-based sorbents.

By contrast, mouldings made from organic materials would have suitable stability, but to date cannot be produced in the same quality as inorganic mouldings produced by the sol-gel process (WO 95/03256). Membranes made from organic polymers can be produced by bulk polymerisation in the presence of a porogen (EP 0 320 023). These polymer membranes are preferably used for the separation of macromolecular substances, such as biopolymers, since macroporous materials can be used for applications of this type. However, mesoporous organic polymers having a nar-

row pore distribution for the separation of smaller molecules cannot be produced in the requisite quality.

5 EP 0 366 252 describes the production of porous organic support materials by a polymeric impression of silica gel particles. The pore system of the silica gel particles is filled with polymer by suspension polymerisation, and monomer and initiator are removed by extraction. A disadvantage in this process is the need for phase separation. In addition, the process merely offers the possibility of producing particulate support materials.

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The object of the present invention was therefore to find a simple production process which enables the production of polymer mouldings having a large specific surface area and a defined pore structure. Materials of this type are particularly suitable for the chromatographic separation of components of low molecular weight.

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It has been found that organic polymer mouldings for chromatography can be produced by bulk polymerisation of monomers in a silica gel moulding followed by removal of the silica gel by dissolution. These polymer mouldings exhibit separation efficiencies which are equivalent to those of silica gel mouldings.

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The present invention accordingly relates to a process for the production of polymeric organic mouldings, characterised by the following process steps:

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- a) provision of a moulding as matrix;
- b) filling of the cavities of the moulding with a monomer solution;
- c) polymerisation of the monomer solution;
- d) removal of the matrix moulding by washing out and dissolution.

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In a preferred embodiment, the matrix moulding used is a silica gel moulding.

In a preferred embodiment, a matrix moulding which has been modified with template molecules is used.

- 5 In a further preferred embodiment, aqueous hydrofluoric acid is used for washing out the matrix moulding.

The present invention also relates to polymeric organic mouldings obtainable by

- 10 a) provision of a moulding as matrix;
 b) filling of the cavities of the moulding with a monomer solution;
 c) polymerisation of the monomer solution;
 d) removal of the matrix moulding by washing out and dissolution.

- 15 In a preferred embodiment, the surfaces of the mouldings have separation effectors.

The present invention also relates to a chromatographic separating column which contains a moulding according to the invention.

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The present invention also relates to the use of a moulding according to the invention in the chromatographic separation of at least two substances.

- 25 For the purposes of the present invention, organic polymeric mouldings are mouldings of any shape, for example membranes or flat or column-shaped mouldings. Flat mouldings have their greatest dimension transverse to the flow direction of the eluent. Particular preference is given to mouldings, such as column-shaped mouldings, which have a dimension of
30 equal length or longer along the axis through which the eluents flow. The size and dimension of the mouldings correspond to the usual dimensions for use in chromatography. Flat mouldings typically have a thickness of

between 0.2 and 20 μm , column-shaped mouldings typically have a diameter of between 0.1 cm and 5 cm and a length (longest dimension) of between 1 and 30 cm. For preparative separations, the stated dimensions can be exceeded in accordance with the dimensions of known column dimensions. For miniaturised applications, the stated dimensions can be reduced into the region of capillaries.

For the purposes of the present invention, organic polymeric mouldings are also mouldings which can be used for a radial column. In this case, the flow through the moulding does not take place along its longitudinal axis. Instead, it has a hole along the longitudinal axis through which the eluent firstly enters the moulding and subsequently exits radially at the periphery. The depth and diameter of the hole depend on the dimensions of the moulding and have the usual magnitude for applications of this type.

Matrix mouldings which are used for the process according to the invention are typically porous mouldings of corresponding dimensions whose pore system is formed, in particular, from macropores. The mouldings preferably additionally also have mesopores in the walls of the macropores. The interconnected macropores typically have a diameter which has a median value of greater than 0.1 μm . The diameter of the mesopores generally has a median value of between 2 and 100 nm. The porosity and specific surface area of the polymerised moulding can be affected by the type of porosity and specific surface area respectively of the matrix moulding. The mouldings according to the invention which are formed may accordingly have macropores and preferably also mesopores having a size in the same order as stated for the matrix mouldings.

Instead of a porous moulding, the matrix moulding used may alternatively be a column or a corresponding holder which is filled with porous particles. In this case, the particle interspaces usually form macropores.

In order to be able to remove the matrix moulding when the polymerisation is complete, the former must be dissolved and washed out without destroying the organic polymer formed. Matrix mouldings made from inorganic materials, such as inorganic oxides, particularly preferably silica gel, are therefore preferably used. These may be, for example, monolithic mouldings, as described in WO 94/19687 or WO 95/03256. They may be employed in calcined or uncalcined form, depending on the desired porosity of the organic polymer to be prepared.

Matrix mouldings made from silica gel can be washed out with aqueous bases or, particularly preferably, with aqueous hydrofluoric acid. If the polymerised organic mouldings are likewise labile under such conditions, another matrix moulding has to be selected. This may be, for example, a porous matrix moulding made from an organic polymer which is washed out under conditions which do not destroy the polymerised moulding. Thus, for example, polylactides or melamine-phenol-formaldehyde resins can be employed.

The process according to the invention enables the production of an extremely wide variety of organic polymeric mouldings. The mouldings can be produced, for example, by free-radical, ionic or thermal polymerisation. These may be, for example, poly(meth)acrylic acid derivatives, polystyrene derivatives, polyesters, polyamides or polyethylenes. The monomers correspondingly to be employed are known to the person skilled in the art in the area of organic polymers. For example, these are monoethylenically or polyethylenically unsaturated monomers, such as vinyl monomers, vinylaromatic and vinylaliphatic monomers, for example styrene and substituted styrenes, vinyl acetates or vinyl propionates, acrylic monomers, such as methacrylates and other alkyl acrylates, ethoxymethyl acrylate and higher analogues, and the corresponding methacrylic acid esters or amides thereof, such as acrylamide, or acrylonitrile. Further monoethyleni-

cally and polyethylenically unsaturated monomers are given, for example, in EP 0 366 252 or US 5,858,296.

5 The person skilled in the art is able correspondingly to combine the various monomers, where appropriate to select a suitable free-radical starter or initiator and thus to put together a monomer solution with which the matrix moulding is filled. The polymerisation duration and temperature are matched to the respective monomer solution in accordance with conventional rules.

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After completion of the polymerisation step, the solid moulding produced, which consists, for example, of the inorganic matrix polymer and the cast organic polymer, is removed, and the material of the matrix moulding is washed out and dissolved out. To this end, the moulding is stored or preferably
15 swirled in a wash solution, optionally with heating. Treatment with aqueous hydrofluoric acid in order to remove silica gel typically takes 48 hours.

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After further washing steps in order to remove the aggressive wash solution and final particles, the porous organic polymeric moulding is obtained as an impression or counterpart to the matrix moulding employed.

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If the mouldings produced already have the suitable functionalities, they can be employed directly for chromatographic separations. For example, a polymer made from polystyrene or derivatives thereof can be used directly for reversed phase separations. To this end, the mouldings are provided with corresponding connectors, surrounded by a casing and integrated into a chromatographic separating column. Suitable holders and casings are already known for inorganic monolithic sorbents (for example

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WO 98/59238 and the unpublished DE 99 32 318) and can be applied to the mouldings according to the invention. Particularly in the case of encasing with plastics, such as, for example, PEEK or fibre-reinforced PEEK,

the organic mouldings according to the invention can usually be encased more effectively and in a more leak-proof manner than the corresponding inorganic mouldings, since they are able to undergo stronger binding to the plastic casing.

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Depending on the separation properties that the moulding according to the invention is to have, however, further modifications may first be necessary. For example, if it is to be employed for affinity or ion-exchange chromatography, the surface must be provided with corresponding separation effectors. In some cases, suitable substances may already have been added to the monomer solution and thus incorporated directly into the polymer.

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Preferably, however, functionalities are firstly introduced during the polymerisation in accordance with known processes and can subsequently be reacted with separation effectors. Further modification can likewise be introduced onto the polymeric mouldings by block or graft polymerisation. Separation effectors and monomers which, besides a polymerisable double bond, also contain further functionalities, such as, for example, oxirane rings, are known to the person skilled in the art. Examples are given in WO 96/2216, WO 96/22316 and WO 95/10354.

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Suitable functionalities of the mouldings according to the invention can likewise be used to bind or immobilise biomolecules, such as, for example, enzymes. Macroporous mouldings are particularly suitable for this purpose. Biomolecules, such as, for example, enzymes, therefore also come under the term separation effectors in accordance with the invention.

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The process according to the invention furthermore enables the production of mouldings having particular separation properties. As in molecular imprinting, template molecules can be bound to the surface of the matrix moulding, which in this case is porous or nonporous. The interspaces or pores are subsequently filled with monomer solution and polymerised to completion. During the polymerisation, cavities form around the template

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molecules. The matrix moulding and the template molecules bound there-
to are then washed out. In contrast to the known processes of molecular
imprinting, the process according to the invention offers the advantage
that, due to the binding to the matrix moulding, the template molecules
5 adopt a position of defined alignment. This results in the formation of cavi-
ties which are more defined and are able to undergo clearer and stronger
interactions during the chromatographic separation. A further major advan-
tage of the process according to the invention is that all template mole-
cules can be washed out after the polymerisation.

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In conventional processes, some of the template molecules are completely
surrounded by the polymer after the polymerisation and can only be re-
moved from the polymer very slowly or not at all. Since template mole-
cules can also be liberated from the polymer during later use of the poly-
15 mers for chromatographic separation and falsify the analysis, the use of
such materials is usually restricted to purification or qualitative analysis.
Trace analysis is virtually impossible.

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Polymers prepared in accordance with the invention do not exhibit this
bleeding. The reason for this is the preferably covalent bonding of the
template molecules to the matrix moulding. In this way, they are never
completely surrounded and held by the polymerised moulding, but instead
are completely removed together with the matrix moulding by the washing-
out of the latter.

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In addition, the preparation of an imprint polymer in accordance with the
prior art requires a large amount of purified template, which can only be
recovered again with difficulty. In the process according to the invention,
by contrast, the template is firstly bonded to the matrix moulding. Excess
30 template molecules can be washed off and collected. It is not until a sec-
ond step that the monomer solution is added and polymerised. The poly-
mer mouldings produced by the process according to the invention using a

template can be both employed as mouldings or, for certain applications, subsequently comminuted to give particles.

5 The process according to the invention thus offers the possibility of producing organic polymeric mouldings of defined porosity. The pores can be defined by the matrix moulding itself or by modification of the matrix moulding with template molecules. The materials according to the invention enable at least equivalent separation efficiencies to be achieved compared with particulate sorbents and do so at a higher flow rate. Both the
10 surface of the matrix moulding and the surface of the moulding according to the invention can be modified, so that there is a multiplicity of ways of matching the mouldings ideally to the respective separation problem.

15 Even without further details, it is assumed that a person skilled in the art will be able to utilise the above description in its broadest scope. The preferred embodiments and examples should therefore merely be regarded as descriptive disclosure which is absolutely not limiting in any way.

20 The complete disclosure content of all applications, patents and publications listed above and below, in particular the corresponding application DE 199 46 674, filed on 29.09.1999, is incorporated into this application by way of reference.

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Examples

1. Production of a polymer moulding using a silica gel matrix moulding

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Material:

4 uncalcined silica gel matrix mouldings (length 11 cm, \varnothing 4 mm)
monomer solution consisting of: 35 ml of styrene, 35 ml of divinylbenzene
(destabilised with NaOH and dried with Na₂SO₄) and
10 0.7 g of azoisobutyronitrile

Equipment:

100 ml single-necked flask,
2 dropping funnels with pressure equalisation
15 drying oven with rotation device

Procedure:

The silica gel matrix mouldings are introduced into a 250 ml dropping funnel lying crosswise and evacuated for 10 minutes. The monomer solution
20 is added dropwise over the course of 2 minutes under reduced pressure. After 10 minutes, when bubble formation is no longer evident, the supernatant polymer solution is poured off, and the mouldings are introduced into the rotary oven, where the polymerisation is carried out at 70°C for 20 hours. After cooling, the parts are introduced into 50% aqueous (v:v) hydrofluoric acid and shaken for 2 days.

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They are subsequently washed with water and 0.5 M phosphate buffer (pH 5.5).

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The organic mouldings produced are then extracted in each case for 6 hours with toluene and acetonitrile. The mouldings are subsequently inserted into a shrink tube and encapsulated with epoxy resin, with HPLC connectors being cast in at the same time.

Polymer moulding data:

mean pore size: 12.2 nm

pore volume: 0.16 cm³

5 mean specific surface area: 50 m² (determined by the BET method)

Chromatographic test:

The number of theoretical plates was determined with toluene:

10 eluent: acetonitrile/water, 60:40

wavelength: 254 nm

Number of theoretical plates: 9935 theoretical plates per m

15 **2. Production of a polymer moulding as impression of a column
packed with silica gel particles**

Procedure:

20 Monospherical silica gel particles (diameter 2 µm) were packed into a Su-
performance column 50 – 10.

In each case, 10 ml of styrene, 10 ml of divinylbenzene and 0.2 g of AIBN
were introduced and reacted at 70°C. After the reaction, the product was
removed and introduced into 50% (v:v) HF solution. The product was sub-
sequently washed with water, phosphate buffer (pH 5.5) (in each case 1
25 hour and 50 ml), methanol, acetone and acetonitrile (100 ml, 10 hours
each).

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